Remarks

Claims 28, 29 and 49 are pending in the subject application. By this Amendment, claims 28 and 49 have been amended to lend greater clarity to the claimed subject matter. Support for these amendments can be found at, for example, page 38 lines 9-28; page 44 lines 3-8; page 44 lines 20-30; page 54 lines 14-19; page 56 lines 21-25; page 59 lines 23-29; and Figures 14, 15 and 16. Accordingly, claims 28, 29 and 49 remain before the Examiner for consideration.

It should be understood that the amendments to the claims have been made solely to expedite prosecution of the subject application to completion and should not be construed as an indication of the applicants' agreement with, or acquiescence in, the rejections of record. Entry and consideration of the amendments presented herein is respectfully requested. Favorable consideration of the pending claims in view of the amendments and remarks set forth herein is earnestly solicited.

The claims currently pending in the subject application are drawn to the applicants' unique system for specifically binding target double stranded polynucleotides. The claims have been amended herein to more clearly delineate the mechanism by which the subject invention achieves its advantageous specificity. The Target Binding Assemblies (TBAs) of the subject invention are made up of multiple nucleic acid recognition units each of which binds without great affinity to discrete target sequences. The multiple nucleic acid recognition sites are directed to discrete sequences on a target double stranded polynucleotide. When all of the multiple nucleic acid recognition sites bind, each with relatively low affinity, to their corresponding target sequences, the combined effect is that the entire TBA (with its multiple nucleic acid recognition units) binds with great affinity and specificity to the target double stranded polynucleotide.

Thus, the effectiveness of TBAs of the subject invention can be attributed to the TBAs having multiple binding components that act cooperatively. Each of these binding components is: a) selective for an individual sequence within the target binding region (TBR), and b) has a "down-shifted" affinity so that it binds with relatively low affinity to its individual binding sequence. Although the individual TBA components bind relatively weakly, the entire TBA binds with great strength as the individual TBA binding components are cooperatively bound together.

The system of the subject invention is particularly unique and advantageous because the TBA binds selectively to a target double stranded polynucleotide, and discriminates for this target

compared to a different (non-target) region, even if the different (non-target) region contains sequences within it which are identical to sequences in the target binding region.

The structural features of the TBA make it possible to, for example, target an individual control region and not interfere with other cellular sites that contain (even exactly identical) individual binding sites that are present in the targeted control region. Specifically exemplified in the subject application is a TBA directed to the HIV-LTR. The exemplified TBA contains a down-shifted binding unit of NF-kB (or binding portion of such) and down-shifted bidning units of SP1. Despite the existence of other sites in the human genome having an NF-kB binding site (e.g., the beta2-micro-globulin promoter, the kappa-light chain promoter, etc.), the TBA for HIV advantageously does not compete for the NF-kb binding sites in the human genome because these other binding sites do not have all of the sequences targeted by the multiple nucleic acid recognition sites of the HIV-LTR TBA.

In view of the unique structural and functional characteristics of the applicants' technology, as reflected by the current claims, the applicants respectfully request favorable consideration of the claims now pending.

Claims 28 and 29 have been rejected under 35 U.S.C. §112, first paragraph. Specifically, the Office Action indicates that claim 28, as amended in the previous Response, contains new matter. The applicants respectfully traverse this grounds for rejection. The applicants agree with the Examiner's observation at pages 2-3 of the outstanding Office Action where it is stated that "[a] particular double stranded sequence could be reasonably a double stranded section of genomic sequence rather than a hybrid made up of a PNA +TNA hybrid." It is true that reference to the "double stranded nucleic acid sequence" can be interpreted to include a double stranded section of genomic sequence as well as a PNA-TNA hybrid. In fact, the inclusion of such a genomic sequence is a specifically contemplated aspect of the subject invention.

It is a basic premise of patent law that the claims must be supported by, and interpreted in accordance with, the disclosure of the invention in the application. As discussed below, the interpretation of claim 28 to include target genomic sequences is clearly supported by the subject specification.

As indicated at page 38, lines 9-11 of the subject specification, the present invention

contemplates both diagnostic and therapeutic applications. Therefore, for purposes of clarity, the applicants' specification is organized along these lines. As a result, an initial section of the disclosure defines a diagnostic system. It is in this section of the application where PNA-TNA hybrids are discussed extensively. However, in addition to the description of diagnostic embodiments, the subject application, and the claims as originally filed, contain ample description of therapeutic and prophylactic uses.

The sections of the subject specification which address therapeutic and prophylactic utilities, make it clear that TBAs can be used to bind directly to an existing duplex nucleic acid sequence. For example, the specification describes the HIV-LTR binding TBA which can be used as a therapeutic agent; in this section of the application, there is no mention of the use of probes to create a PNA-TNA hybrid. Rather, in these embodiments of the invention, TBAs bind to existing (including genomic) double stranded DNA segments. Thus, for example, the HIV-LTR is double stranded and acts as a TBR. *See, e.g.*, lines 9-28 of page 38:

> 10. Therapeutic applications. Because of the very tight and selective nucleic acid binding characteristics of the novel TBAs described herein, therapeutic utilities are contemplated in addition to the diagnostic utilities of these compounds. Thus, a TBA comprising tight and specific binding for the HIV-LTR, by virtue of having an NF-kB p50 and an SPI DNA recognition unit in close association (see Figure 10, HIV-Detect II) is useful to bind up the HIV-LTR and thereby prevent transcription from this key element of the HIV genome. The unique features of the assembly sequences of the TBA allow recombinant vectors to introduce DNA encoding such a TBA into a cell and the proper folding of the expressed sequences. Once inside the cell, the nuclear localization signals of the p50 subunit directs the transport of the TBA to the nucleus where it binds tightly to the LTR of any integrated HIV, effectively shutting the pathogen down.

There is no mention of the use of probes. Rather, it is clear that the TBA binds the HIV-LTR directly.

Further evidence of the applicants' envisioning the use of the subject invention to bind with genomic DNA is in the description of the expression of the TBAs *in vivo*. In this embodiment of the subject invention, the TBAs are not even fully formed until they are expressed in the cell and bind to their target double stranded DNA. Again, no probes are used. One example of this embodiment of the subject invention is described in detail at page 44, lines 20-30 of the subject invention:

> 11. A method of assembling multimeric TBAs *in vivo* which comprises introducing nucleic acids encoding component TBAs into a cell. ...Upon *in vivo* expression of each component TBA and proximal binding, via the nucleic acid recognition unit of each component TBA to nucleic acid sequences encountered in the nucleus or elsewhere in the cell, component expressed TBAs are directed to assemble via the included assembly and asymmetry sequences into multimeric TBAs. As described above, such multimeric TBAs will have the advantage of binding specifically with high affinity to TBRs in a specific target sequence, but not at all or with very low affinity to cousin nucleic acids.

There is no mention of probes because it is understood that the binding sites are already present in the cell.

As an additional matter, the drawings included in the application are considered part of the disclosure and should not be overlooked in aiding in the interpretation of the claims. The Federal Circuit has recognized that "drawings alone may provide a 'written description' of an invention as required by Section 112." *Vas-Cath Inc. v. Mahurkar*, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991); *In re Kaslow*, 217 USPQ 1089, 1096 (Fed. Cir. 1983). Similarly, in those instances where a visual representation can clarify the words in the claim, the drawings may be used in the same way as the written specification to provide evidence relevant to claim interpretation. *See Autogiro Co. of Am. v. United States*, 155 USPQ 697, 703 (Ct.Cl. 1967). To this end, Figure 14 shows TBAs specific to binding sites in the HIV-LTR, and Figure 15 shows TBAs "specific to the binding sites in the HPV genome." (Emphasis added). It is well known in the art that the HIV-LTR is double-stranded. *See, e.g.,* Genes V, Lewin, B., pages 1039-1040, Oxford University Press and Cell Press (1994). Furthermore, it is also well known that the HPV genome is double-stranded DNA. In Example 13, page 56, lines 11-25, there is a description of how to express and combine the parts of "an HIV-LTR binding TBA," such that "the TBA occurs to form a complex which tightly and specifically binds the HIV LTR":

> For this purpose, it is desirable to select sequences encoding DNA binding domains such that the expressed monomers are assembled into a TBA which does not bind to natural human sequences. Thus, it is only upon binding of the TBA components to their target sequences that association between all components of the TBA occurs to form a complex which tightly and specifically binds the HIV LTR.

Therefore, the applicants' previous amendment to claim 28 does not constitute new matter and is clearly supported by the subject specification, wherein it is taught that the TBR to which the TBA is directed may be a double-stranded genomic nucleic acid. Accordingly, the applicants respectfully request reconsideration and withdrawal of this rejection.

Claims 28, 29, and 49 have been rejected under 35 U.S.C. §112, second paragraph, as failing to particularly and definitely point out and distinctly claim the instant invention. As with the "new matter" rejection set forth under 35 U.S.C. §112, first paragraph, this rejection is based on the premise that the application, as filed, does not describe the binding of TBAs to genomic double stranded DNA. Please note that the applicants' claims have been amended to lend greater clarity to the claimed subject matter. Also, as explained in detail above, the application does, in fact, provide specific descriptions of the use of TBAs to bind to double stranded polynucleotides without the need to use probes (PNAs). Thus, a person skilled in the art would have no difficulty in understanding the metes and bounds of the applicants' claims.

It is well settled that the language of the claims is to be read in light of the specification. *See Allen Archery Inc. v. Browning Mfg. Co.*, 2 USPQ2d 1490, 1494 (Fed. Cir. 1987). It has been further stated that "if the claims, read in light of the specification, reasonably apprise those skilled in the art both of the utilization and scope of the invention, and if the language is as precise as the subject matter permits, the courts can demand no more." *North Am. Vaccine, Inc. v. American Cyanamid Co.*, 7 F.3d 1571, 28 USPQ2d 1333, 1339 (Fed. Cir. 1993).

Thus, the applicants respectfully traverse this grounds for rejection because a person skilled in the art, having the benefit of the applicants' disclosure, would have no difficulty in ascertaining the metes and bounds of the claims as submitted herewith. Therefore, the applicants respectfully request reconsideration and withdrawal of the rejection set forth under 35 U.S.C. §112, second paragraph.

Claim 29 has been rejected under the second paragraph of 35 U.S.C. §112 as being confusing when read in conjunction with claim 28 from which claim 29 depends. The applicants do not agree that there should be any confusion regarding the meaning of claim 29; however, in order to lend greater clarity to the claimed subject matter, claim 28 has been amended to more succinctly describe the applicants' invention.

It is well settled in the law that a patent application need not disclose that which is well known in the art. *See In re Myers*, 228 USPQ2d 940 (Fed. Cir. 1986). In fact, what is well-known is best omitted. The applicants respectfully submit that the person of ordinary skill in the art, having the benefit of the teachings of the subject application, would be able to readily discern the metes and bounds of the current claims. One embodiment of the invention pertains to the use of a recombinant vector for expression of the functional TBAs. It is well known in the art that a starting methionine is not a necessary element of these functional units. As a result, one of ordinary skill in the art would appreciate that the referenced sequence listings represent a minimum blueprint of the protein. The addition of a methione as needed for expression would be a matter of routine practice by those skilled in the art. In any event, the claims have been amended to eliminate any possible source of confusion.

Claim 28 has been rejected under 35 U.S.C. §103(a) as being unpatentable over Frankel *et al.* The subject invention is highly advantageous in that it provides materials and methods which can bind to target sequences with great specificity. The current claims are drawn to methods wherein a TBA specifically and selectively binds to target sequences but, advantageously does not bind to non-target sequences. Notably, the TBAs can bind to their target sequences without binding to closely related "cousin" sequences. These cousin sequences may contain identical binding sites that are also found in the target binding site. In one example a TBA for the HIV-LTR (with its two adjacent NF-kB binding sites next to three adjacent SP1 binding sites) discriminates from other sites containing identical NF-kB binding sites.

The method of the subject invention is by no means obvious and, in fact, is counterintuitive because it involves making the binding portions bind with less affinity to achieve greater overall specificity. Advantageously, the method of the subject invention can be used to target control regions without interfering with normal cellular trafficking. This result is summarized on page 54, lines 14-19 and graphically demonstrated in Figure 16 of the application as filed. This is crucial because most control regions have DNA binding sites that are also contained in non-target control regions. The use of the TBAs to target such control regions is very unique and advantageous. Frankel et al. do not teach or suggest this.

The Frankel *et al.* molecules simply bind to all E2 binding sites while the TBAs of the subject invention distinguish individual E2 binding sites. The criticality of being able to distinguish between different E2 sites can be seen with respect to the Human Papilloma Virus. The strains HPV-16, HPV-18 and HPV-33 contain multiple sequences for E2 to bind (i.e., ACCNNNNNNGGT). In HPV-16 (Genebank, AF125673, HPV-16), for example, there is a region with two identical adjacent E2 binding sites (base pairs 35-46 and 50-61) and one region with a single E2 binding site (base pairs 7450-7461). The design of the TBA provides a method for targeting any of these sites without interfering with any of the other sites. Such a unique and advantageous functionality is not disclosed or suggested by Frankel *et al.*

As acknowledged in the applicants' parent application, U.S.S.N. 08/353,476, such unexpected specificity can be the basis for establishing the non-obviousness of an invention. In the Reasons for Allowance for the claims in that case, the Examiner observed that:

> [w]hile the prior art teaches the use of several different types of sequence-specific DNA-binding proteins to detect hybridization between a target nucleic acid sequence and a perfectly matched probe, no prior art has been found teaching or suggesting a sequence-specific nucleic acid-binding molecule or assembly (called a "TBA" or "BBA" in the instant application) capable of stabilizing perfect hybrids, and discriminating between perfect hybrids and those having one or more mismatches due to hybridization with a non-target nucleic acid"(emphasis in original).

While the claims in the '476 application pertain to the applicants' diagnostic embodiments and the current claims pertain to therapeutic uses, the specificity remains highly unexpected and advantageous, and not suggested by the cited references. As discussed above, the subject application teaches both the diagnostic use of TBAs to distinguish perfect hybrids from non-perfect hybrids and the use of TBAs to distinguish target from non-target sequences when the non-target sequences contain a portion of the sequence contained in the target. This second capability is critical for the therapeutic use of TBAs as claimed in the subject application. It is in such therapeutic uses that it is essential for the TBA to bind to target sequences but not to similar non-target sequences. The advantageous specificity of the TBAs, as currently claimed, is not disclosed or suggested by Frankel *et al.* Therefore, the applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. §103 based on the Frankel *et al.* reference.

Claim 49 has been rejected under 35 U.S.C. §103(a) as being unpatentable over Essigmann *et al.* The applicants respectfully traverse this grounds for rejection because the Essigmann *et al.* reference describes technology which is functionally and structurally distinct from the current invention.

Essigmann *et al.* describe using heterobifunctional compounds where the first agent binds to cellular DNA to form a genomic lesion and the second agent is used to block DNA repair of the lesion caused by the first agent. Thus, the "second agent" of Essigmann *et al.* is not a nucleic acid recognition unit as required by the applicants' claims. Furthermore, there would be no reason for one skilled in the art to modify the Essigmann *et al.* teachings to arrive at the subject invention since the purpose of the "second agent" as described by Essigmann *et al.* is to "protect" the DNA lesion caused by the "first agent." Furthermore, nothing in the Essigmann *et al.* reference teaches or suggests the advantageous selectivity achieved using the system of the subject invention.

Although a TBA of the subject invention may be comprised of two or more parts, the function of the TBA parts, both as separate entities as well as the entire cooperatively-bound whole, are different than the parts of the Essigmann *et al.* heterobifunctional compounds. As noted above, Essigmann *et al.* describe heterobifunctional compounds where the first agend binds to the cellular DNA to form a genomic lesion and the second agent is used to block DNA repair of the first agent lesion. While a TBA may be also used to bind to cellular DNA and prevent DNA repair, it does so in a very different manner. The multiple binding parts of the TBA provide binding specificity that is not present nor suggested by Essigmann *et al.* Essigmann *et al.* neither teach nor suggest how to selectively target binding regions which include identical binding regions found in the genome.

It has been well established in the patent law that the mere fact that the purported prior art could have been modified or applied in some manner to yield applicant's invention it would not have made the modification or application obvious unless the prior art suggested the desirability of the modification. *In re Gordon*, 221 USPQ 1125,1127 (Fed. Cir. 1984). However, as expressed by the CAFC, to support a §103 rejection, "[b]oth the suggestion and the expectation of success must be founded in the prior art ..." *In re Dow Chemical Co.* 5 USPQ 2d 1529, 1531 (Fed. Cir. 1988). As is clearly shown by the foregoing remarks, one finds neither the suggestion nor the expectation of success in the cited reference. An assertion of obviousness without the required suggestion or

expectation of success in the prior art is tantamount to using applicant's disclosure to reconstruct the prior art to arrive at the subject invention. Hindsight reconstruction of the prior art cannot support a §103 rejection, as was specifically recognized by the CCPA in *In re Sponnoble*, 56CCPA 823, 160 USPQ 237, 243 (1969). Therefore, the applicants respectfully request the reconsideration and withdrawal of the rejection under 35 U.S.C. § 103 based on the Essigmann *et al.* reference.

The subject specification has been objected to because of informalities. Attached with this amendment are new formal drawings in which the use of lower case letters corresponds to the descriptions provided in the specification. No new matter is being introduced by the submission of the new drawings.

In view of the foregoing remarks and amendments to the claims, the applicants believe that the currently pending claims are in condition for allowance, and such action is respectfully requested.

The Commissioner is hereby authorized to charge any fees under 37 CFR §§1.16 or 1.17 as required by this paper to Deposit Account No. 19-0065.

The applicants invite the Examiner to call the undersigned if clarification is needed on any of this response, or if the Examiner believes a telephonic interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,

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Attachment: Petition and Fee for Extension of Time
Marked-Up Version of Amended Claims
Formal Drawings (29 pages total)

Marked-Up Version of Amended Claims

Claim 28 (four times amended):

A method of using a target binding assembly (TBA) [comprising at least one] wherein said TBA comprises a plurality of nucleic acid [recognition unit] recognitions units, and optionally one or all of the sequences selected from the group consisting of a linker sequence, an assembly sequence, an asymmetry sequence, and a nuclear localization signal sequence (NLS) [and an optional support attachment (OSA)]; wherein the combined binding affinity of said plurality of nucleic acid recognition units is such that said TBA specifically binds to a target double stranded nucleic acid sequence but does not bind to non-target sequences; wherein [said TBA is administered to a patient in need of such treatment] said method comprises administering to a patient a therapeutically or prophylactically effective amount of said TBA, [which comprises administering the TBA, either in the form of a purified protein complex or in the form of a recombinant vector which, upon entry into the patient is able to express the TBA,] such that the TBA binds a [particular] target double stranded nucleic acid sequence to achieve [the] a desired prophylactic or therapeutic result.

Claim 49 (amended):

A method of assembling multimeric target binding assemblies (TBAs) *in vivo* or *in situ* which comprises introducing [component] components of said multimeric TBAs into a cell, said [component TBAs] components each comprising a [DNA] nucleic acid recognition unit, and optionally comprising assembly sequences, asymmetry sequences, nuclear localization signal sequences, and linker sequences, such that upon proximal binding via the [DNA] nucleic acid recognition unit of each component [TBA] to nucleic acid sequences encountered in the nucleus or elsewhere in the cell, [component TBAs] the components assemble into multimeric TBAs; wherein the combined binding affinity of said components is such that said assembled multimeric TBA specifically binds to a target double stranded nucleic acid sequence but does not bind to non-target sequences.